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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,992	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *91602 & 112702*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 11-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of colon cancer, does not reasonably provide enablement for the treatment of all other diseases embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to 'a method for inhibiting Aurora-2 kinase; GSK-3; Src; etc. activity' and 'a method of treating diseases mediated by Aurora-2, GSK-3, etc.' which according to specification is drawn to a therapeutic use, e.g., in treating different cancers, Alzheimer's disease, multiple sclerosis, etc. (see pages 17-21). First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test assays and procedures are provided in the specification pages 311-320 related to aurora-2 kinase, GSK-3, Src inhibition, wherein the inhibitory activity data (K_i) for some of the compounds of the invention is provided, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the disorders of the instant claims. The disorders encompassed by the instant claims include proliferative disorders

or cancers which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of proliferative diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. "How sister kinetochores attach to microtubules from opposite spindle poles during mitosis (bi-orientation) remains poorly understood", see Tanaka et al. (PubMed Abstract enclosed). Also, Rogers et al., express that "How the selective release of chromosome cohesion is regulated during meiosis remains unclear". This is clearly indicative of the fact that the therapeutic role of these kinase inhibitors is very speculative.

A 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term

covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Further, neurodegenerative diseases covers diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994).

Further, the list of the diseases includes multiple sclerosis which has traditionally been very difficult or impossible to treat effectively with chemotherapeutic agents. See e.g., Casanova et al. (PubMed Abstract enclosed) state that "Multiple Sclerosis (MS) is a disorder in which the pathogenesis is not clearly understood", see the abstract. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or lessening the severity' effect of a 'disease' solely based on the inhibitory activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the

invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

2. Claims 1-7 and 9-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound **or** a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for the entire scope of the recitation "pharmaceutically acceptable **derivatives**". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims recite "A compound ... or a pharmaceutically acceptable **derivative** or **prodrug** thereof" wherein there is insufficient description in the specification regarding the types of derivatives intended by the recitation. The specification on page 28, lines 12-26 the term 'pharmaceutically-acceptable derivative' is defined as 'salt, ester .... or a metabolite or residue thereof", which is extremely broad. For example, the specification does not provide which 'which salt of an ester or other derivative that are capable of providing the compound of the invention' are intended. The generic formulae of the claims already include both esters and the corresponding free acid forms, see e.g., in the definition of R^3, the term " CO_2R " wherein R is defined to be H, alkyl, etc. There is no disclosure regarding any other esters that are capable of providing compounds of the invention. Similarly, the term "metabolite", "residue" are not sufficiently described. A metabolite is any compound which is pharmaceutically active *in vivo*

when it undergoes 'metabolic' process and the specification does not provide any disclosure of what these compounds might be that *in vivo* transform in to the instantly claimed compounds.

Also, prodrugs in general (and as noted in specification page 28), 'that increase the bioavailability of the compound'. In that sense recitation of prodrug is acceptable. It is also known that many examples of "prodrugs" include 'esters' that may hydrolyzed *in vivo* to the acids. However, the definition of various substituent groups in formula IIIc already include such groups, i.e., acids as well as esters. The specification does not provide what other 'compounds' of the invention are intended to be prodrugs. In addition, it is not clear whether compounds bearing these groups are excluded from being a potential "prodrug". If compounds bearing these groups, which are likely to undergo *in vivo* transformation, are excluded then what is included in the definition of 'prodrug' and where on the compound of formula IIIc, these groups are placed, is not clear.

It is suggested that the recitation "pharmaceutically acceptable **derivative or prodrug**" be replaced with -- pharmaceutically acceptable salt thereof --.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-5 and 9-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Armistead et al., WO 01/60816 (published August 23, 2001). The instant claims read on reference disclosed compound, see compounds 1, 5-8, 33-35, etc. The compounds are disclosed to be useful as pharmaceutical therapeutic agents having kinase inhibitory activity, see the abstract.

2. Claims 1-5 and 9-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Pease et al., WO 01/64655 (published September 7, 2001). The instant claims read on reference disclosed compound, see compound 119. The compounds are disclosed to be useful as pharmaceutical therapeutic agents having kinase inhibitory activity, see the abstract.

Note: Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application(s) upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims of this application. Particularly, the provisional application does not support the structural formula IIIc with the variables $R^{2'}$, L-Z-R^3, etc.Claims 1-5 and 9-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bradbury et al., WO 00/39101. The instant claims read on reference disclosed compound, see the compound of Example 135 (pages 85-86). The reference discloses that the compounds are useful as pharmaceutical therapeutic agents having kinase inhibitory activity, see pages 51-52.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al., WO 00/39101. The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula I in page 2 and the species of Example 135. The compounds are taught to be useful as kinase inhibitors useful as pharmaceutical therapeutic agents, see pages 51-55. claims 1-5 and 9-27 are anticipated by the reference as indicated in the 102 rejection above. Claims 6-8 differ from the reference by reciting a more limited genus and/or species of the reference genus. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful

compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Receipt is acknowledged of the Information Disclosure Statements filed on September 16 and November 27, 2002 and copies are enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Deepak Rao
Primary Examiner
Art Unit 1624

March 22, 2004